REMARKS

Claims 32-71 and 73-80 are currently pending in the Application. Claims 32-34, 36, 39-71 and 73-80 are under examination. Claims 32 and 57 are amended herein to correct typographical errors.

In the Office Action mailed December 30, 2009, the Examiner maintained several rejections, which for clarity are listed below in the order in which they are addressed herein:

1. Claim(s) 32, 34, 35, 37-41, 48-54, 57, 60, 61, 63-65, 73-75, 76- and 78, stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Ledford et al. J Mol Diagn. 2000 May;2(2):97-104) in view of Dattagupta et al. (U S. Patent Number 5,215,899), Lane et al. (US. 5,770,365), Prudent et al. (US. 5,985,557), Rather (US. 5,858,367), (U.S. 5,593,835), and Lau et al. Science. 26 October 2001. Vol. 294: Pages 858-862),

2. Claim(s) 33, 36, 44-47, 58, 59, 62, and 68-71 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Ledford et al. (J Mol Diagn. 2000 May;2(2):97-104) in view of Lane et al. (US. 5,770,365), in view of Prudent et al. (US. 5,985,557), Dattagupta et al. (U S. Patent Number 5,215,899), Rather (US. 5,858,367), (US. 5,593,835), and Lau et al. (Science. 26 October 2001. Vol. 294: Pages 858-862), as applied to claim(s) 32 and 57, and in further view of Morris et al. J Clin Microbiol. 1996 Dec;34(12):2933-6),

3. Claim(s) 42, 43, 66, and 67 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Ledford et al. (J Mol Diagn. 2000 May;2(2):97-104) in view of Lane et al. (US. 5,770,365), in view of Prudent et al. (US. 5,985,557), Dattagupta et al. (U S. Patent Number 5,215,899), Rather (U.S. 5,858,367), (US. 5,593,835), and Lau et al. (Science. 26 October 2001. Vol. 294: Pages 858-862), as applied to claim(s) 32 and 57, and in further view of Marras et al.)Genet Anal. 1999 Feb;14(5-6):151-6),

4. Claim(s) 55, 56, 79, and 80 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Ledford et al. (J Mol Diagn. 2000 May;2(2):97-104) in view of Lane et al. (US. 5,770,365), in view of

Prudent et al. (US. 5,985,557), Dattagupta et al. (U S. Patent Number 5,215,899), Rather (U.S. 5,858,367), (US. 5,593,835), and Lau et al. (Science. 26 October 2001. Vol. 294: Pages 858-862), as applied to claim(s) 32 and 57, and in further view of Hyldig-Nielsin et al. (US. 5,985,563),

5. Claims 32-34, 36, 39-71, 73-80 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 21-23 and 29-33 of copending Application No. 11/929,878, and

6. Claims 32-34, 36, 39-71, 73-80 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-12, and 15-18 of copending Application No. 11/809,567.

The Claims Are Not Obvious

1. Claim(s) 32, 34, 35, 37-41, 48-54, 57, 60, 61, 63-65, 73-75, 76- and 78, stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Ledford et al. J Mol Diagn. 2000 May;2(2):97-104) in view of Dattagupta et al. (U S. Patent Number 5,215,899), Lane et al. (US. 5,770,365), Prudent et al. (US. 5,985,557), Rather (US. 5,858,367), (U.S. 5,593,835), and Lau et al. Science. 26 October 2001. Vol. 294: Pages 858-862),

As the Board of Patent Appeal and Interferences has recently confirmed, a proper obviousness determination requires that an Examiner make "a searching comparison of the claimed invention – *including all its limitations* – with the teaching of the prior art." *See In re Wada and Murphy*, Appeal 2007-3733, *citing In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis in original). Further, the necessary presence of all claim features is axiomatic, since the Supreme Court has long held that obviousness is a question of law based on underlying factual inquiries, including … ascertaining the differences between the claimed invention and the prior art. *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) (emphasis added). Indeed, Section 904 of the MPEP instructs Examiners to conduct an art search that covers "the invention *as described and*

claimed." (emphasis added). Lastly, Applicants respectfully direct attention to MPEP § 2143, the instructions of which buttress the conclusion that obviousness requires at least a suggestion of all of the features of a claim, since the Supreme Court in *KSR Int'l v. Teleflex Inc.* stated that "there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (*quoting In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

In sum, it remains well-settled law that obviousness requires at least a suggestion of all of the features in a claim. *See In re Wada and Murphy*, *citing CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) and *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)).

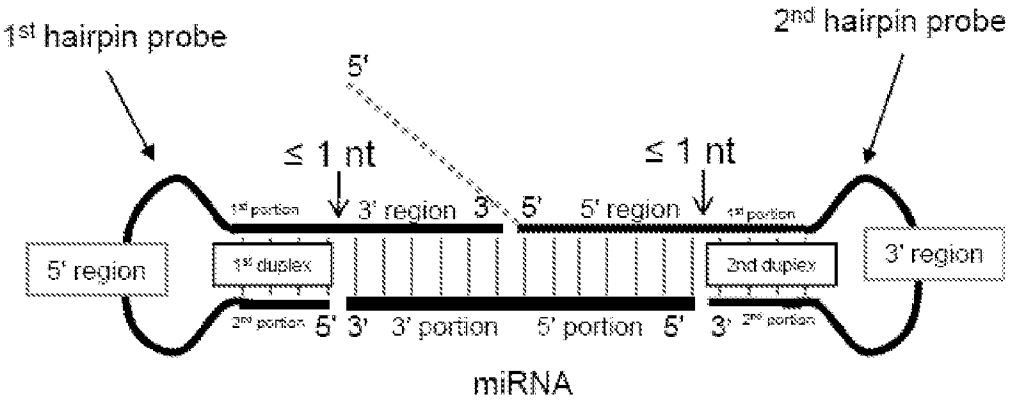
None of the cited references teach or suggest formation of a detection structure that comprises two hairpin probes that have the features of the probes of the instant claims, and that both hybridized to a target nucleic acid to from a detection structure as specified in the instant claims.

Making reference to a microRNA that has a 3' portion and a 5' portion, Claims 32 and 57 recite hairpin probes having the following features:

i) a first hairpin probe comprising a 3' region that is complementary the 3' portion of the microRNA, and a 5' region that is not complementary to the microRNA, wherein a first portion of the 5' region is complementary to a second portion of the 5' region, wherein the first portion and the second portion of the 5' region hybridize to each other to form a first duplex when said hairpin probe is hybridized to the microRNA, and wherein the first duplex and said 3' region of the probe are within one nucleotide of each other; and

ii) a second hairpin probe comprising a 5' region that is complementary to the 5' portion of the microRNA and a 3' region that is not complementary to said microRNA, wherein a first portion of the 3' region is complementary to a second portion of the 3' region, wherein the first portion and the second portion of said 3' region hybridize to each other to form a second duplex when said hairpin probe is hybridized to the microRNA, and wherein the second duplex and the 5' region of the probe are within one nucleotide of each other;

Such a structure is shown, *e.g.*, in Figure 2. A structure similar to that in Figure 2, but labeled to show the features of the two hairpin probes and the detection structure as recited in the claims is shown in the diagram below:



The claims recite that each probe comprises a region that is not complementary to the miRNA, and that forms a duplex (the 1st and 2nd duplexes in the 1st and 2nd hairpin probes, respectively, shown above). In addition, the claims recite the 1st duplex formed by the 1st hairpin probe is within one nucleotide of the region of the 1st hairpin probe that is complementary to the 3' portion of the miRNA (the "3' region" of the 1st hairpin probe). Similarly, the 2nd duplex formed by the 2nd hairpin probe must be within one nucleotide of the region of the 2nd hairpin probe that is complementary to the 5' portion of the miRNA (the "5' region" of the 2nd hairpin probe). The dotted line in the figure above shows and embodiment in which the 2nd hairpin probe comprises additional sequence on the 5' end, *e.g.*, as diagrammed in original Figure 2.

The Examiner asserts that Dattagupta teaches the use of two hairpin probes for RNA detection, pointing to column 9, line 22 (Office communication, page 5). Applicants respectfully disagree. Dattagupta describes an amplification method involving use of a second set of hairpin probe/second probe pairs that are complementary to *the RNA transcripts* formed by transcribing from the first hairpin probe - target nucleic

acid complex. Dattagupta does not teach or suggest formation of a single complex in which both a first and second hairpin molecule hybridize to the same target nucleic acid, as recited in the instant claims. While not acquiescing that Dattagupta teaches or suggests use of two hairpin molecules in a single complex of any description, Applicants respectfully point out that none of Ledford, Dattagupta, Lane, Prudent, Rather or Lau teach or suggest the use of two hairpin probes that have the features discussed above, and that form the dumbbell structure recited in the instant claims.

While Applicants do not acquiesce that other conditions necessary for establishing prima facie obviousness have been met, Applicants submit that the combination of Ledford, Dattagupta, Lane, Prudent, Rather and Lau does not teach or suggest all the features of Claims 32 and 57, or the claims depending therefrom, *i.e.*, Claims 34, 35, 37-41, 48-54, 60, 61, 63-65, 73-75, 76- and 78. The cited art therefore fails to establish prima facie obviousness of these claims and Applicants respectfully request that these rejections be withdrawn.

2. Claim(s) 33, 36, 44-47, 58, 59, 62, and 68-71 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Ledford et al. (J Mol Diagn. 2000 May;2(2):97-104) in view of Lane et al. (US. 5,770,365), in view of Prudent et al. (US. 5,985,557), Dattagupta et al. (U S. Patent Number 5,215,899), Rather (US. 5,858,367), (US. 5,593,835), and Lau et al. (Science. 26 October 2001. Vol. 294: Pages 858-862), as applied to claim(s) 32 and 57, and in further view of Morris et al. J Clin Microbiol. 1996 Dec;34(12):2933-6),

Applicants discuss the shortcomings of the combination of Ledford, Lane, Dattagupta, Prudent, Rather and Lau above. Morris discloses a TaqMan RT-PCR assay comprising use of a fluorescent probe configured for FRET detection. Morris fails to cure the deficiencies of the combination of Ledford, Lane, Dattagupta, Prudent, Rather and Lau. As discussed above, Claims 32 and 57 recite, *inter alia*, formation of an RNA detection structure in which the first and second hairpin probes have specific recited features, and that form a dumbbell structure when hybridized to a microRNA. Morris does not teach or suggest the use of two hairpin probes that have the features discussed

above, and that form the dumbbell structure recited in the instant claims. Thus, the combination of Ledford, Lane, Prudent, Dattagupta, Rather, Lau, and Morris fails to teach each element of Claims 33, 36, 44-47, 58, 59, 62, and 68-71, and fails to establish prima facie obviousness of these claims. Applicants therefore respectfully request that these rejections be withdrawn.

3. Claim(s) 42, 43, 66, and 67 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Ledford et al. (J Mol Diagn. 2000 May;2(2):97-104) in view of Lane et al. (US. 5,770,365), in view of Prudent et al. (US. 5,985,557), Dattagupta et al. (U S. Patent Number 5,215,899), Rather (U.S. 5,858,367), (US. 5,593,835), and Lau et al. (Science. 26 October 2001. Vol. 294: Pages 858-862), as applied to claim(s) 32 and 57, and in further view of Marras et al.)Genet Anal. 1999 Feb;14(5-6):151-6),

Applicants discuss the shortcomings of the combination of Applicants discuss the shortcomings of the combination of Ledford, Lane, Dattagupta, Prudent, Rather and Lau above. Marras teaches the use of multiplex reactions to detect dingle-nucleotide variations using molecular beacon probes. Marras fails to cure the deficiencies of the combination of Ledford, Lane, Dattagupta, Prudent, Rather and Lau. Claims 32 and 57 recite, *inter alia*, formation of an RNA detection structure in which the first and second hairpin probes have specific recited features, and that form a dumbbell structure when hybridized to a microRNA. Marras does not teach or suggest the use of two hairpin probes that have the features discussed above, and that form the dumbbell structure recited in the instant claims. Thus, the combination of Ledford, Lane, Dattagupta, Prudent, Rather, Lau, and Marras fails to teach each element of Claims 42, 43, 66, and 67, and fails to establish prima facie obviousness of these claims. Applicants therefore respectfully request that these rejections be withdrawn.

4. Claim(s) 55, 56, 79, and 80 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Ledford et al. (J Mol Diagn. 2000 May;2(2):97-104) in view of Lane et al. (US. 5,770,365), in view of Prudent et al. (US. 5,985,557), Dattagupta et al. (U S. Patent Number 5,215,899), Rather (U.S. 5,858,367), (US. 5,593,835), and Lau et al.

(Science. 26 October 2001. Vol. 294: Pages 858-862), as applied to claim(s) 32 and 57, and in further view of Hyldig-Nielsin et al. (US. 5,985,563).

Applicants discuss the shortcomings of the combination of Applicants discuss the shortcomings of the combination of Ledford, Lane, Prudent, Dattagupta, Rather and Lau above. Hyldig-Nielsen discloses the detection of ribosomal RNA using peptide nucleic acid probes. Hyldig-Nielsen fails to cure the deficiencies of the combination of Ledford, Lane, Dattagupta, Prudent, Rather and Lau. Claims 32 and 57 recite, *inter alia*, formation of an RNA detection structure in which the first and second hairpin probes have specific recited features, and that form a dumbbell structure when hybridized to a microRNA. Hyldig-Nielsen not teach or suggest the use of two hairpin probes that have the features discussed above, and that form the dumbbell structure recited in the instant claims. Thus, the combination of Ledford, Lane, Dattagupta, Prudent, Rather, Lau, and Hyldig-Nielsen fails to teach each element of Claims 55, 56, 79, and 80, and fails to establish prima facie obviousness of these claims. Applicants therefore respectfully request that these rejections be withdrawn.

5-6 Claims 32-34, 36, 39-71, 73-80 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 21-23 and 29-33 of copending Application No. 11/929,878, and Claims 32-34, 36, 39-71, 73-80 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-12, and 15-18 of copending Application No. 11/809,567.

These applications are commonly owned with the present application. Applicants respectfully request that these rejections be held in abeyance pending a determination that one or more claims in the instant application is allowable.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that all grounds for rejection have been addressed and Applicants' claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at 608-662-1277.

Dated: April 21, 2010

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